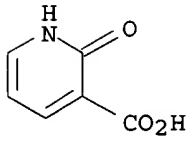
10

L14 ANSWER 13 OF 13 REGISTRY COPYRIGHT 2003 ACS on STN
RN 609-71-2 REGISTRY
CN 3-Pyridinecarboxylic acid, 1,2-dihydro-2-oxo- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Nicotinic acid, 1,2-dihydro-2-oxo- (6CI, 7CI)
OTHER NAMES:
CN 1,2-Dihydro-2-oxo-3-pyridinecarboxylic acid
CN 1,2-Dihydro-2-oxonicotinic acid
CN 2-Hydroxy-3-carboxypyridine
CN **2-Hydroxynicotinic acid**
CN 2-Hydroxypyridine-3-carboxylic acid
CN 3-Carboxy-2-pyridone
CN NSC 226152
FS 3D CONCORD
MF C6 H5 N O3
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, MEDLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

214 REFERENCES IN FILE CA (1907 TO DATE)
17 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
214 REFERENCES IN FILE CAPLUS (1907 TO DATE)
11 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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SL54 (chem7 — L56

d bib ab ind 25

L57 ANSWER 25 OF 26 CA COPYRIGHT 2003 ACS on STN
AN 72:119676 CA
TI Uptake and metabolism of nicotinic acid by human blood platelets. Effects of structure analogs and metabolic inhibitors
AU Gaut, Zane N.; Solomon, Harvey M.
CS Spec. Treat. Unit, Martland Hosp., Newark, NJ, USA
SO Biochimica et Biophysica Acta (1970), 201(2), 316-22
CODEN: BBACAQ; ISSN: 0006-3002
DT Journal
LA English
AB Human platelets incubated for 1 hr at 37.degree. with nicotinic acid-7-14C (10 micromoles) accumulated the radioactivity with a gradient, (dpm per ml intraplatelet water)/(dpm per ml incubation **medium**), of approx. 20. The uptake process involved incorporation of the isotope into compds. such as NAD which do not readily diffuse from the cell. Of the total radioactivity inside, nicotinic acid represented approx. 3.9%, nicotinamide, 2.6%; NAD, 17.7%; and other products, 75.8%. Such synthesis and accumulation of radioactivity was variously inhibited by a number of analogs of nicotinic acid as well as by dinitrophenol, NaF, salicylate, and NaCN. Of the analogs studied, **2-hydroxynicotinic acid** was the most potent. It reduced the gradient of radioactivity to 1.4 at 1mM and inhibited isotopic incorporation into the compds. previously described. These data suggest that **2-hydroxynicotinic acid** inhibits one or more of the early reactions in the biosynthesis of NAD and nicotinamide. Nicotinamide-7-14C was neither accumulated nor metabolized by the platelet.
CC 15 (Pharmacodynamics)
ST nicotinate metabolism platelets; metabolism nicotinate platelets; platelets nicotinate metabolism; uptake nicotinate platelets
IT Blood platelets
(nicotinic acid metabolism by, analogs and metabolic inhibitors effect on)
IT Absorption, biological
(of nicotinic acid, by blood platelets)
IT 59-67-6, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, by blood platelets, analogs and metabolic inhibitors effect on)
IT 51-28-5, biological studies 69-72-7, biological studies 89-00-9 100-55-0 110-86-1, biological studies 143-33-9 393-55-5 499-81-0 500-22-1 583-08-4 586-98-1 609-70-1 **609-71-2** 872-85-5 2398-81-4 5326-23-8 7681-49-4, biological studies 10128-92-4 10177-29-4 22620-27-5 27805-12-5 27828-71-3
RL: BIOL (Biological study)
(nicotinic acid metabolism inhibition by, in blood platelets)

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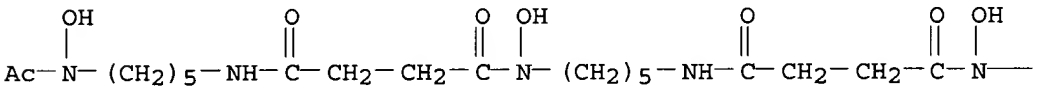
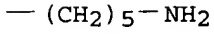
L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 70-51-9 REGISTRY
CN Butanediamide, N'-[5-[[4-[[5-(acetylhydroxyamino)pentyl]amino]-1,4-dioxobutyl]hydroxyamino]pentyl]-N-(5-aminopentyl)-N-hydroxy- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propionohydroxamic acid, N-[5-[3-[(5-aminopentyl)hydroxycarbamoyl]propionamido]pentyl]-3-[[5-(N-hydroxyacetamido)pentyl]carbamoyl]- (8CI)
OTHER NAMES:
CN 3,9,14,20,25-Pentaazatriacontane-2,10,13,21,24-pentone, 30-amino-3,14,25-trihydroxy-
CN 30-Amino-3,14,25-trihydroxy-3,9,14,20,25 pentaazatriacontane-2,10,13,21,24-pentaone
CN Deferoxamin
CN **Deferoxamine**
CN Deferoxamine B
CN Deferriferrioxamine B
CN Deferrioxamine
CN Deferrioxamine B
CN Desferan
CN Desferex
CN Desferin
CN Desferioxamine B
CN Desferrin
CN Desferrioxamine
CN Desferrioxamine B
CN N-[5-[3-[(5-Aminopentyl)hydroxycarbamoyl]propionamido]pentyl]-3-[[5-(N-hydroxyacetamido)pentyl]carbamoyl]propionohydroxamic acid
CN NSC 527604
FS 3D CONCORD
DR 7278-84-4
MF C25 H48 N6 O8
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIUDB, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

PAGE 1-A



PAGE 1-B



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2228 REFERENCES IN FILE CA (1907 TO DATE)

196 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2233 REFERENCES IN FILE CAPLUS (1907 TO DATE)
46 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

L35 ANSWER 7 OF 11 CA COPYRIGHT 2003 ACS on STN
AN 104:82038 CA
TI **1-Hydroxy-2-pyridone** derivatives as virucides
IN Yoshino, Kazuhiro; Arima, Masatoshi; Sadai, Masanao; Oba, Kenkichi
PA Lion Corp., Japan
SO Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 60215626	A2	19851029	JP 1984-69177	19840409
PRAI JP 1984-69177		19840409		

AB **1-Hydroxy-2-pyridone** derivs. (I) or their salts (R1 = H, C1-23 alkyl, alkenyl, etc.; R2 and R4 = H, C1-9 alkyl, halogen, Ph, etc.; R3 = H, C1-23 alkyl, cycloalkyl, etc.) are effective virucides against herpes simplex virus. Thus, I (R1 = C13H27; R2 = H; R3 = Me; R4 = H) added at a concn. of 0.5 .mu.g/mL to a **culture medium** contg. herpes simplex virus inhibited viral growth completely.

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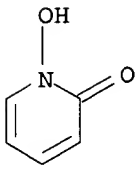
not on CDROM

5

1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS on STN
RN 822-89-9 REGISTRY
CN 2(1H)-Pyridinone, 1-hydroxy- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2(1H)-Pyridone, 1-hydroxy- (6CI, 7CI, 8CI)
OTHER NAMES:
CN 1-Hydroxy-2(1H)-pyridinone
CN 1-Hydroxy-2(1H)-pyridone
CN 1-Hydroxy-2-pyridinone
CN **1-Hydroxy-2-pyridone**
CN N-Hydroxy-2-pyridone
FS 3D CONCORD
DR 119167-17-8
MF C5 H5 N O2
CI COM
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, IFICDB, IFIPAT, IFIUDB, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

124 REFERENCES IN FILE CA (1907 TO DATE)
54 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
124 REFERENCES IN FILE CAPLUS (1907 TO DATE)
7 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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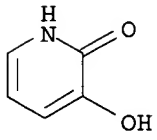
SL32(deu) = L34

3/8 ? Dame

L11 ANSWER 5 OF 5 REGISTRY COPYRIGHT 2003 ACS on STN
RN 16867-04-2 REGISTRY
CN 2(1H)-Pyridinone, 3-hydroxy- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2(1H)-Pyridone, 3-hydroxy- (7CI, 8CI)
CN 2,3-Pyridinediol (6CI)
OTHER NAMES:
CN 2,3-Dihydroxypyridine
CN 3-Hydroxy-1H-pyridin-2-one
CN 3-Hydroxy-2(1H)-pyridinone
CN 3-Hydroxy-2-pyridinone
CN **3-Hydroxy-2-pyridone**
CN NSC 49272
FS 3D CONCORD
DR 13466-42-7, 119764-03-3
MF C5 H5 N O2
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHEM, DDFU, DRUGU, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MSDS-OHS, RTECS*, SPECINFO, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

305 REFERENCES IN FILE CA (1907 TO DATE)
43 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
305 REFERENCES IN FILE CAPLUS (1907 TO DATE)
5 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

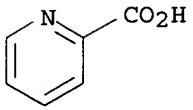
S L24 (chem) ;

product 1

L27 ANSWER 23 OF 37 CA COPYRIGHT 2003 ACS on STN
AN 110:150013 CA
TI Release of iron from ferritin molecules and their iron-cores by 3-hydroxypyridinone chelators in vitro
AU Brady, M. C.; Lilley, K. S.; Treffry, A.; Harrison, P. M.; Hider, R. C.; Taylor, P. D.
CS Krebs Inst. Biomol. Res., Univ. Sheffield, Sheffield, S10 2TN, UK
SO Journal of Inorganic Biochemistry (1989), 35(1), 9-22
CODEN: JIBIDJ; ISSN: 0162-0134
DT Journal
LA English
AB Ferritin mols. contain 24 subunits forming a shell around an inorg. Fe-core. Release of Fe(III) from ferritin and its isolated Fe-cores by a series of hydroxypyridinone chelators with high affinities for Fe(III) was compared. The results collectively suggest that the chelators act by penetrating the protein shell and interacting directly with the Fe-core in ferritin. Fe(III) is probably removed bound to a single ligand, but once outside the protein shell, the trihydroxypyridinone Fe(III) complex predominates. The order of effectiveness of a group of pyridinones found for Fe removal from ferritin mols. in soln. differs from that obtained with hepatocytes in **culture** or with whole animals, where membrane soly. and other factors may modulate the response.

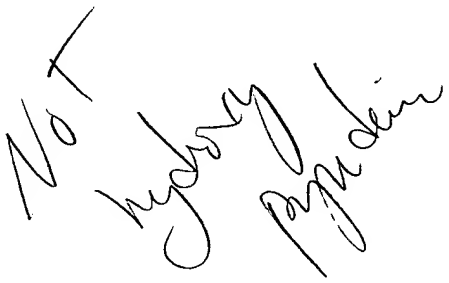
> d

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 98-98-6 REGISTRY
CN 2-Pyridinecarboxylic acid (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Picolinic acid (7CI, 8CI)**
OTHER NAMES:
CN .alpha.-Pyridinecarboxylic acid
CN 2-Carboxypyridine
CN 2-Pyridylcarboxylic acid
CN NSC 171
CN o-Pyridinecarboxylic acid
FS 3D CONCORD
MF C6 H5 N O2
CI COM
LC STN Files: AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

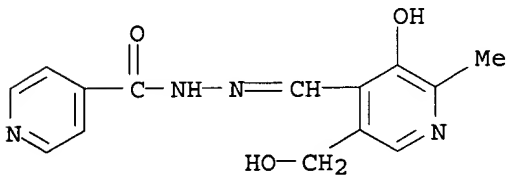


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2635 REFERENCES IN FILE CA (1907 TO DATE)
250 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2640 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)



L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 737-86-0 REGISTRY
CN 4-Pyridinecarboxylic acid, [[3-hydroxy-5-(hydroxymethyl)-2-methyl-4-pyridinyl]methylene]hydrazide (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Isonicotinic acid, hydrazide, hydrazone with pyridoxal (6CI)
CN Isonicotinic acid, [[3-hydroxy-5-(hydroxymethyl)-2-methyl-4-pyridyl]methylene]hydrazide (7CI, 8CI)
OTHER NAMES:
CN NSC 77674
CN PIH
CN **Pyridoxal isonicotinoyl hydrazone**
FS 3D CONCORD
DR 82845-52-1
MF C14 H14 N4 O3
CI COM
LC STN Files: ADISNEWS, AGRICOLA, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, DDFU, DRUGU, EMBASE, MEDLINE, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

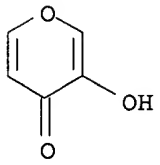


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

119 REFERENCES IN FILE CA (1907 TO DATE)
19 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
121 REFERENCES IN FILE CAPLUS (1907 TO DATE)
12 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

2

L4 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2003 ACS on STN
RN 496-63-9 REGISTRY
CN 4H-Pyran-4-one, 3-hydroxy- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN **3-Hydroxy-4-pyrone**
CN 3-Hydroxy-4H-pyran-4-one
CN 3-Hydroxypyran-4-one
CN NSC 78608
CN Pyrocomenic acid
CN Pyromeconic acid
FS 3D CONCORD
MF C5 H4 O3
LC STN Files: AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAOLD, CAPLUS, CASREACT, CHEMLIST, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, NAPRALERT, SPECINFO, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

145 REFERENCES IN FILE CA (1907 TO DATE)
17 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
145 REFERENCES IN FILE CAPLUS (1907 TO DATE)
20 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

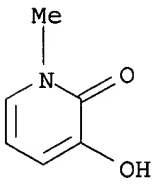
=>

S L4 <chem> = L21

free of cat = 102

7

L6 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 19365-01-6 REGISTRY
CN 2(1H)-Pyridinone, 3-hydroxy-1-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2(1H)-Pyridone, 3-hydroxy-1-methyl- (8CI)
OTHER NAMES:
CN 1-Methyl-3-hydroxy-2-pyridinone
CN **1-Methyl-3-hydroxypyrid-2-one**
CN 3-Hydroxy-1-methyl-2-pyridone
CN N-Methyl-3-hydroxy-2-pyridone
FS 3D CONCORD
MF C6 H7 N O2
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, MEDLINE, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

46 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
46 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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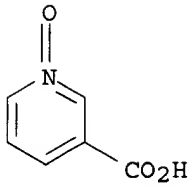
L46<dup7 L48

See 7 102 and 5

9

L12 ANSWER 10 OF 11 REGISTRY COPYRIGHT 2003 ACS on STN
RN 2398-81-4 REGISTRY
CN 3-Pyridinecarboxylic acid, 1-oxide (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Nicotinic acid, 1-oxide (6CI, 7CI, 8CI)
OTHER NAMES:
CN 3-Carboxypyridine N-oxide
CN 3-Pyridinecarboxylic acid oxide
CN N-Hydroxynicotinic acid
CN **Nicotinic acid N-oxide**
CN Nicotinic acid oxide
CN NSC 93890
CN Oxiniacic acid
CN Pyridine-3-carboxylic acid N-oxide
FS 3D CONCORD
DR 2758-22-7
MF C6 H5 N O3
CI COM
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, DDFU, DRUGU, HODOC*, IFICDB, IFIPAT, IFIUDB, MRCK*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

222 REFERENCES IN FILE CA (1907 TO DATE)
10 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
222 REFERENCES IN FILE CAPLUS (1907 TO DATE)
32 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

L9 Chem> L52

L53 ANSWER 9 OF 14 CA COPYRIGHT 2003 ACS on STN
AN 119:40849 CA
TI Growth inhibition of **cultured** animal cells with nicotinic acid related compounds
AU Taguchi, Hiroshi; Ueda, Satoshi; Nishito, Yasumasa; Okumura, Katsuzumi; Shimabayashi, Yoshihide
CS Fac. Bioresour., Mie Univ., Japan
SO Bulletin of the Faculty of Bioresources, Mie University (1992), 8, 51-7
CODEN: BFBUEF; ISSN: 0915-0471
DT Journal
LA Japanese
AB Effect of nicotinic acid-related compds. on the growth of **cultured** animal cells was investigated. Each compd. was added at various concns. (1 .mu.M-0.1 M) to the **culture medium** of murine myeloid cells (P3X63-Ag8.653), syrian hamster kidney cells (BHK-21 clone-13) and human leukemia cells (K-562). All of the compds. tested were more or less inhibitory to every cells. When compared at 10 mM, it can be summarized as below: In murine myeloid cells, trigonelline had no effect; **nicotinic acid N-oxide** and cinchomeronic acid were very weak inhibitors; nicotinic acid, 6-hydroxynicotinic acid, etc. were weak inhibitors; nicotinamide, isonicotinic acid hydrazide, picolinamide, pyridoxamine, N1-methylnicotinamide, pyridoxine, etc. were strong inhibitors; picolinic acid, dipicolinic acid, pyridoxal and pyridoxal 5'-phosphate were strongest inhibitors (no living cell was detectable). The apparent inhibition with nicotinamide at 5 mM was recovered when the compd. was removed from the **medium** after 48 h incubation. On the contrary, large amt. of cells were killed with other potent inhibitors at 5 mM after 48 h incubation. In syrian hamster kidney cells, the effect of above inhibitors were generally weaker than those in murine myeloid cells. In human leukemia cells, the inhibition pattern was similar to that in murine myeloid cells with the exception of trigonelline.
CC 1-12 (Pharmacology)
Section cross-reference(s): 18
ST nicotinate analog cell growth
IT Animal cell
(growth of **cultured**, nicotinic acid-related compds. inhibition of, of humans and lab. animals)
IT 54-47-7, Pyridoxal 5'-phosphate 54-85-3, Isonicotinic acid hydrazide 59-67-6, Nicotinic acid, biological studies 65-23-6, Pyridoxine 66-72-8, Pyridoxal 85-87-0, Pyridoxamine 89-00-9, Quinolinic acid 93-60-7 98-92-0, Nicotinamide 98-96-4, Pyrazinamide 98-97-5, Pyrazinecarboxylic acid 98-98-6, Picolinic acid 100-26-5, Isocinchomeronic acid 114-33-0, N'-Methylnicotinamide 462-08-8, 3-Aminopyridine 490-11-9, Cinchomeronic acid 499-81-0, Pyridine-3,5-dicarboxylic acid 499-83-2, Dipicolinic acid 535-83-1, Trigonelline 1452-77-3, Picolinamide **2398-81-4**, **Nicotinic acid N-oxide** 3106-60-3, N1-Methylnicotinamide 5006-66-6, 6-Hydroxynicotinic acid
RL: BIOL (Biological study)
(**cultured** cell growth inhibition by, of humans and lab. animals)

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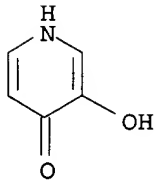
4

L9 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2003 ACS on STN
RN 1121-23-9 REGISTRY
CN 4(1H)-Pyridinone, 3-hydroxy- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4(1H)-Pyridone, 3-hydroxy- (7CI, 8CI)
OTHER NAMES:
CN 3-Hydroxy-4(1H)-pyridinone
CN 3-Hydroxy-4(1H)-pyridone
CN **3-Hydroxy-4-pyridone**
CN 3-Hydroxyl-4(1H)-pyridone
CN Pyrocomene amine acid
FS 3D CONCORD
MF C5 H5 N O2
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, PROMT, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

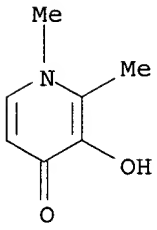
125 REFERENCES IN FILE CA (1907 TO DATE)
45 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
127 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

128 (chem) = L32

6

L9 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2003 ACS on STN
RN 30652-11-0 REGISTRY
CN 4(1H)-Pyridinone, 3-hydroxy-1,2-dimethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4(1H)-Pyridone, 3-hydroxy-1,2-dimethyl- (8CI)
OTHER NAMES:
CN 1,2-Dimethyl-3-hydroxy-4(1H)-pyridinone
CN **1,2-Dimethyl-3-hydroxy-4-pyridone**
CN 1,2-Dimethyl-3-hydroxypyridin-4-one
CN 1,2-Dimethyl-3-hydroxypyridine-4-one
CN 3-Hydroxy-1,2-dimethyl-4(1H)-pyridinone
CN 3-Hydroxy-1,2-dimethyl-4-pyridinone
CN 3-Hydroxy-1,2-dimethyl-4-pyridone
CN CGP 37391
CN CP 20
CN CP 20 (chelating agent)
CN Deferione
CN Deferiprone
CN Ferriprox
CN L 1
CN L 1 (chelating agent)
FS 3D CONCORD
MF C7 H9 N O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CIN, CSCHEM, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, GMELIN*, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

360 REFERENCES IN FILE CA (1907 TO DATE)
20 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
364 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

L36<chem7> = L38

L45 ANSWER 9 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 134:110234 CA
TI Iron chelators inhibit the growth and induce the apoptosis of kaposi's sarcoma cells and of their putative endothelial precursors
AU Simonart, Thierry; Degraef, Chantal; Andrei, Graciela; Mosselmans, Roger; Hermans, Philippe; Van Vooren, Jean-Paul; Noel, Jean-Christophe; Boelaert, Johan R.; Snoeck, Robert; Heenen, Michel
CS Department of Dermatology, Erasme University Hospital, Brussels, B-1070, Belg.
SO Journal of Investigative Dermatology (2000), 115(5), 893-900
CODEN: JIDEAE; ISSN: 0022-202X
PB Blackwell Science, Inc.
DT Journal
LA English
AB Iron is suspected to be involved in the induction and/or progression of various human tumors. More particularly, iron may be involved in the pathogenesis of Kaposi's sarcoma, a tumor of probable vascular origin. This study was designed to investigate the effect of iron deprivation on Kaposi's sarcoma. The effects of iron chelators and iron deprivation assocd. with serum withdrawal were investigated on Kaposi's sarcoma-derived spindle cells, on a transformed Kaposi's sarcoma cell line (Kaposi's sarcoma Y-1) and on endothelial cells, which are the probable progenitors of Kaposi's sarcoma cells. Desferrioxamine and deferiprone, two chem. unrelated iron chelators, induced a time- and concn.-dependent inhibition of endothelial and Kaposi's sarcoma cell growth. The inhibition of cell growth was assocd. with a decrease in Ki-67 and in both stable and total proliferating cell nuclear antigen expression. Inhibition of the progression through the G1-phase of the cell cycle was further evidenced by decreased expression of cyclin D1 and of p34 cyclin-dependent kinase 4. Terminal deoxynucleotidyl transferase-mediated desoxyuridine-triphosphate nick end labeling assay, flow cytometry with annexin-V-fluorescein and morphol. anal. indicated that iron chelation also induced a time- and concn.-dependent apoptosis. This apoptotic effect was prevented by the addn. of exogenous iron. Induction of iron deprivation in the **culture medium** by serum withdrawal led to similar cell cycle effects, which, however, could only be partly reverted by the addn. of exogenous iron. In conclusion, these results show that iron deprivation inhibits the growth and induces the apoptosis of Kaposi's sarcoma cells and of their putative endothelial precursors. This suggests that iron chelators may represent a potential therapeutic approach for the treatment of Kaposi's sarcoma.
RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L45 ANSWER 10 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 131:662 CA
TI Cardioprotective effect of .alpha.-tocopherol, ascorbate, deferoxamine, and deferiprone: mitochondrial function in **cultured**, iron-loaded heart cells
AU Link, Gabriela; Konijn, Abraham M.; Hershko, Chaim
CS Department of Human Nutrition and Metabolism, Hebrew University Faculty of Medicine, Jerusalem, Israel
SO Journal of Laboratory and Clinical Medicine (1999), 133(2), 179-188
CODEN: JLCMAK; ISSN: 0022-2143
PB Mosby, Inc.
DT Journal
LA English
AB Because mitochondrial inner membrane respiratory complexes are important targets of iron toxicity, we used iron-loaded rat heart cells in **culture** to study the beneficial effect on mitochondrial enzymes of the iron chelators deferoxamine (DFO) and deferiprone (L1) and of antioxidants and reducing agents (ascorbate and .alpha.-tocopherol). Reduced NAD-cytochrome c oxidoreductase (complex I-III) and succinate

dehydrogenase were the most-sensitive indicators of iron toxicity and cardioprotective effect. Although at concns. below 0.3 mmol/L the iron-mobilizing effect of L1 was less than that of DFO, both were equally effective in protecting or restoring mitochondrial respiratory enzyme activity. At 1.0 mmol/L, L1 toxicity was manifested in respiratory enzyme inhibition, whereas DFO had no such effect. Ascorbate (0.057 to 5.7 mmol/L) had a mild cardioprotective effect at the highest concn. only, in assocn. with decreased cellular iron uptake. By contrast, .alpha.-tocopherol (0.023 mmol/L) completely inhibited mitochondrial iron toxicity without affecting iron uptake or release, and irresp. of whether it was used before, during, or after in vitro iron loading. These observations illustrate the usefulness and limitations of iron chelators and other agents used for preventing iron toxicity to the heart and other vital organs, and they underline the need for exploring in more detail the effects of these agents in the clin. setting.

RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L45 ANSWER 13 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 129:197710 CA
TI Antiproliferative effect of deferiprone on the Hep G2 cell line
AU Chenoufi, Norchen; Drenou, Bernard; Loreal, Olivier; Pigeon, Christelle; Brissot, Pierre; Lescoat, Gerard
CS Liver Research Unit, INSERM U49, Pontchaillou University Hospital, Rennes, 35033, Fr.
SO Biochemical Pharmacology (1998), 56(4), 431-437
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science Inc.
DT Journal
LA English
AB Fe is an essential element in cellular metab. and the growth of all living species, and is involved in DNA replication. The risk of hepatocellular carcinoma development is assocd. with an increase in Fe availability. The aim of the present work was to investigate the effect of an oral Fe chelator, deferiprone (CP20), on HepG2 cell-line proliferation in **culture**. HepG2 cell **cultures** were maintained in the absence of fetal calf serum (FCS) and in the presence or not (control **cultures**) of CP20 at the concns. of 50 or 100 .mu.M; deferoxamine (DFO) was used as an Fe chelator ref. Cell proliferation was investigated by the anal. of DNA synthesis using [3H] methyl-thymidine incorporation and of the cell cycle by flow cytometry. Fe chelation efficiency in the **culture** model was studied by analyzing the effect of CP20 on radioactive Fe uptake, intracellular ferritin level, and transferrin receptor expression. CP20, at the concn. of 50 or 100 .mu.M, inhibited DNA synthesis after 48 h of incubation and induced an accumulation of the cells in the S phase of the cell cycle. Fe chelators inhibited cellular Fe uptake, decreased intracellular ferritin level, and increased transferrin receptor protein and mRNA levels. The results show that CP20 as well as deferoxamine inhibit HepG2 cell proliferation and block cell cycle in the S phase.

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L45 ANSWER 15 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 127:60376 CA
TI Chelation and mobilization of cellular iron by different classes of chelators
AU Zanninelli, G.; Glickstein, H.; Breuer, W.; Milgram, P.; Brissot, P.; Hider, R. C.; Konijn, A. M.; Libman, J.; Shanzer, A.; Cabantchik, Z. Ioav
CS Department of Biological Chemistry, Institute of Life Sciences, Hebrew University of Jerusalem, Jerusalem, 91904, Israel
SO Molecular Pharmacology (1997), 51(5), 842-852
CODEN: MOPMA3; ISSN: 0026-895X
PB Williams & Wilkins

DT Journal
LA English
AB Iron chelators belonging to three distinct chem. families were assessed in terms of their physicochem. properties and the kinetics of iron chelation in soln. and in two biol. systems. Several hydroxypyridinones, reversed siderophores, and desferrioxamine derivs. were selected to cover agents with different iron-binding stoichiometry and geometry and a wide range of lipophilicity, as detd. by the octanol-water partition coeffs. The selection also included highly lipophilic chelators with potentially cell-cleavable ester groups that can serve as precursors of hydrophilic and membrane-impermeant chelators. Iron binding was detd. by the chelator capacity for restoring the fluorescence of iron-quenched calcein (CA), a dynamic fluorescent metallosensor. The iron-scavenging properties of the chelators were assessed under three different conditions: (a) in soln., by mixing iron salts with free CA; (b) in resealed red cell ghosts, by encapsulation of CA followed by loading with iron; and (c) in human erythroleukemia K562 cells, by loading with the permeant CA-acetomethoxy ester, in situ formation of free CA, and binding of cytosolic labile iron. The time-dependent recovery of fluorescence in the presence of a given chelator provided a continuous measure for the capacity of the chelator to access the iron/CA-contg. compartment. The resulting rate consts. of fluorescence recovery indicated that chelation in soln. was comparable for the members of each family of chelators, whereas chelation in either biol. system was largely dictated by the lipophilicity of the free chelator. For example, desferrioxamine was among the fastest and most efficient iron scavengers in soln. but was essentially ineffective in either biol. system when used at .ltoreq.200 .mu.M over a 2-h period at 37.degree.. The highly lipophilic and potentially cell-cleavable hydroxypyridinones and reversed siderophores were highly efficient in all biol. systems tested. It is implied that in K562 cells, hydrolysis of these chelators is relatively slower than their ingress and binding of intracellular iron. The chelator-mediated translocation of iron from cells to **medium** was assessed in 55Fe-transferrin loaded K562 cells. The speed of iron mobilization by members of the three families of chelators correlated with the lipophilicity of the free ligand or the iron-complexed chelator. The acquired information is of relevance for the design of chelators with improved biol. performance.

L45 ANSWER 17 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 125:211951 CA
TI Up-regulation of vascular endothelial growth factor production by iron chelators
AU Beerepoot, Laurens V.; Shima, David T.; Kuroki, Masatoshi; Yeo, Kaing-Teck; Voest, Emile E.
CS Dep. Int. Med. Med. Oncol., Univ. Hosp. Utrecht, Utrecht, 3508 GA, Neth.
SO Cancer Research (1996), 56(16), 3747-3751
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB Agents that modulate cellular iron availability have been studied for their antitumor activity. Based on encouraging in vitro studies, the iron chelator deferoxamine (DFO) has been used in clin. studies to treat cancer patients. The observation that DFO induced macular edema in several cancer patients led to the present investigation of vascular endothelial growth factor (VEGF) as a possible mediator of the encountered side effects. Both normal and malignant cell lines were incubated with DFO and a variety of other iron chelators. DFO, at concns. achievable in humans, induced a 3-5-fold increase in VEGF mRNA expression in all cell lines studied. This increased VEGF mRNA expression was dose and time dependent. A panel of structurally different iron chelators induced an even more potent increase in VEGF mRNA expression. The DFO-induced increase in VEGF mRNA expression translated into 6- and 4-fold increases in VEGF protein secretion in conditioned **media** of retinal pigment epithelial and

C6 glioblastoma cells, resp. These findings suggest that VEGF may act as a mediator of the side effects induced by iron chelation therapy. In addn., because VEGF is an important regulator of angiogenesis, iron chelators should be given with caution to cancer patients.

L45 ANSWER 19 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 123:188523 CA
TI Inhibition of iron toxicity in rat and human hepatocyte **cultures** by the hydroxypyridin-4-ones CP20 and CP94
AU Chenoufi, Norchen; Hubert, Noeella; Loreal, Olivier; Morel, Isabelle; Pasdeloup, Nicole; Cillard, Josiane; Brissot, Pierre; Lescoat, Gerard
CS INSERM U49, Unite Recherches Hepatologiques, Rennes, Fr.
SO Journal of Hepatology (1995), 23(2), 166-73
CODEN: JOHEEC; ISSN: 0168-8278
PB Munksgaard
DT Journal
LA English
AB The protective effect of the hydroxypyridin-4-one (CP20 and CP94) was studied on iron-loaded rat and human hepatocytes; desferrioxamine B was used as a chelator ref. Iron load was achieved by addn. of 5 up to 50 .mu.M iron citrate to the **culture medium**. One day after iron treatment, an increase in lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase and malondialdehyde extracellular concns. was measured in rat and human hepatocyte **cultures**. This enzyme release and the increase in free extracellular malondialdehyde were obsd. with 5 .mu.M iron and high levels were obtained with 50 .mu.M. The bidentate chelators CP20 and CP94 (150 .mu.M) appeared to be as effective as the hexadentate chelator desferrioxamine (50 .mu.M) in the protection of rat and human hepatocytes against the toxic effect of iron load achieved by culturing the cells for 1 day in the presence of 50 .mu.M iron citrate. In rat and human hepatocytes **culture** for 1 day in the presence of 1 .mu.M 55Fe-50 .mu.M iron citrate plus CP20, CP94 or desferrioxamine B, a decrease of iron uptake by the cells was obsd. When the hepatocytes were **cultured** for 1 day in the presence of 1 .mu.M 55Fe-50 .mu.M iron citrate and then for a further day in the presence of CP20 , CP94 or desferioxamine B but not iron, the chelators decreased the intracellular iron level, indicating their iron releasing effect from the loaded cells. The obsd. effects of the hydroxypyridin-4-ones CP20 and CP94 were as potent as the effect of desferrioxamine B. This study present new data favoring the potential clin. interest of this new class of chelating agents in the treatment of human iron overload.

L45 ANSWER 22 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 122:123069 CA
TI EPR study of antioxidant activity of the iron chelators pyoverdin and hydroxypyrid-4-one in iron-loaded hepatocyte **culture**: comparison with that of desferrioxamine
AU Morel, Isabelle; Sergent, Odile; Cogrel, Pascale; Lescoat, Gerard; Pasdeloup, Nicole; Brissot, Pierre; Cillard, Pierre; Cillard, Josiane
CS Lab. Biol. Cell. Veg., UFR Sci. Pharmaceutiques, Rennes, Fr.
SO Free Radical Biology & Medicine (1995), 18(2), 303-10
CODEN: FRBMEH; ISSN: 0891-5849
PB Elsevier
DT Journal
LA English
AB Iron supplementation of hepatocyte **culture** induced the prodn. of lipid-derived radicals as shown by spin-trapping with .alpha.-(4-pyridyl 1-oxide)-N-tert-butylnitrone (POBN). The EPR signal corresponding to POBN/lipid-derived radicals (aN = 15.6 G aH = 2.6 G) was concn. dependent on iron (Fe-NTA) added to the **culture medium** (50, 100, 200 .mu.M). It was also incubation times dependent (0 to 24 h). The EPR signal could be used as a marker for iron-induced lipid peroxidn. The antioxidant activity of two iron chelators, pyoverdin (Pa) and

hydroxypyrid-4-one deriv. (CP20) was compared with that of desferrioxamine (DFO) on iron-loaded hepatocyte **culture**. These compds. (100 .mu.M) were tested either in pretreatment or simultaneously with Fe-NTA (100 .mu.M). In each procedure, the EPR signal obtained from the cells supplemented with iron was substantially reduced in the presence of either DFO or CP20 but not with Pa. Moreover, the DFO and CP20 but not Pa showed protective effect on the leakage of the intracellular enzyme lactate dehydrogenase into the **culture medium**. The present study described a specific spin-trapping technique in conjunction with EPR spectroscopy that is able to demonstrate the cytoprotective effect of iron chelators, as shown by the elimination of lipid-derived radicals in iron-loaded hepatocyte **culture**.

L45 ANSWER 24 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 122:1015 CA
TI Iron transport and subcellular distribution in Hep G2 hepatocarcinoma cells
AU Parkes, Joel G.; Templeton, Douglas M.
CS Department Clinical Biochemistry, University Toronto, Toronto, ON, M5G 1L5, Can.
SO Annals of Clinical and Laboratory Science (1994), 24(6), 509-20
CODEN: ACLSCP; ISSN: 0091-7370
DT Journal
LA English
AB Thalassemic patients with iron overload are presently treated with deferoxamine or the exptl. chelator deferiprone. To understand how these agents remove iron from the liver, **cultured** human hepatoma cells loaded with iron were previously used as a model for hepatic iron overload. The present study was undertaken to characterize further the pathways of iron transport and distribution in these cells. The activation energy for Fe2+ transport is 19 kJ/mol greater than for Fe3+, and the rate of Fe2+ transport-but not that of Fe3+ -decreases with temp. above 25.degree.C, suggesting distinct uptake processes for different redox states of iron. Iron loading, which promotes a greater rate of Fe3+ transport, also caused a proportionally greater deposition of iron in the microsomal and cytosolic compartments and specifically lowered the activities of succinate-cytochrome c reductase and 5'-nucleotidase, representative markers of the mitochondria and plasma membrane, resp. Both deferiprone and deferoxamine decreased total cellular iron and iron in each fraction except cytosol, indicating mobilization of iron for clearance from the cell via the cytosol. This model may be useful in characterizing the determinants of effective chelation in patients.

L45 ANSWER 25 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 121:245566 CA
TI Ability of the orally effective iron chelators dimethyl- and diethyl-hydroxyprid-4-one and of deferoxamine to restore sarcolemmal thiolic enzyme activity in iron-loaded heart cells
AU Link, Gabriela; Pinson, Arie; Hershko, Chaim
CS Hadassah Med. Sch., Hebrew Univ., Jerusalem, Israel
SO Blood (1994), 83(9), 2692-7
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English
AB In view of the profound functional and structural abnormalities shown in the authors' previous studies in **cultured**, iron-loaded rat heart cells, the authors have examd. the ability of the orally effective iron chelators dimethyl-3-hydroxypyrid-4-one (DMHP or L1) and diethyl-3-hydroxy-pyrid-4-one (DEHP or CP94) and of deferoxamine (DF) to reverse the damage caused by iron loading to heart cell organelles. At a concn. of 1.0 mmol/L, all three iron chelators were equally efficient in removing iron and restoring the activity of the thiolic sarcolemmal enzymes 5'-nucleotidase and Na,K,ATPase. However, at 0.1 mmol/L DMHP and DEHP were less effective than DF both in their iron-mobilizing effect and

in promoting thiolic enzyme recovery. The superior efficiency of DF at low concns. illustrates the advantage of the hexadentate chelating action of DF as compared with bidentate chelators such as DMHP and DEHP requiring a 3 to 1 molar ratio to iron for optimal effect. In contrast to its beneficial effect on sarcolemmal enzyme activity, iron chelation was unable to reverse the increase in .beta.-hexosaminidase activity caused by abnormal lysosomal fragility. The authors' study demonstrates for the first time that iron-induced peroxidative damage to the myocardial cell is assocd. with a marked loss of Na,K,ATPase activity, an enzyme with a major role in the maintenance of cellular resting potential. The timing of this damage and the restoration of Na,K,ATPase function by iron-chelating treatment suggest a cause-and-effect relation between the obsd. injury to the sarcolemmal enzyme and the reversible electrophysiol. abnormalities obsd. in the same heart **culture** system in the authors' previous studies.

L45 ANSWER 26 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 121:221417 CA
TI Differential toxicity of .alpha.-keto hydroxypyridine iron chelators and desferrioxamine to human hemopoietic precursors in vitro
AU Cunningham, J. M.; Al-Refaie, F. N.; Hunter, A. E.; Sheppard, L. N.; Hoffbrand, A. V.
CS Mol. Cell Pathol. Unit, R. Free Hosp. Sch. Med., London, NW3 2PF, UK
SO European Journal of Haematology (1994), 52(3), 176-9
CODEN: EJHAEC; ISSN: 0902-4441
DT Journal
LA English
AB Compliance with iron chelation therapy improves life expectancy in transfusion-dependent haematol. disorders. However, failure of compliance with parenteral desferrioxamine (DF) therapy and the expense incurred makes this drug unavailable for most patients in the developing world. The authors have been evaluating the orally active iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L1) in both preclin. and clin. trials. Five patients have developed reversible agranulocytosis during treatment with this agent. The authors have now studied the effects of L1, other .alpha.-ketohydroxypyridines and DF on bone marrow myeloid progenitors using the CFU-GM system. The results show that L1 is less toxic than DF to normal bone marrow myeloid progenitors (ID50:130 .mu.mol/L vs. 7.9 .mu.mol/L). The L1 ID50 is within the previously reported range of peak plasma values (80-450 .mu.mol/L). When satg. concns. of iron were added to the **cultures**, the mean toxicity of all the chelators was significantly decreased over the range of doses tested, e.g. L1 ID50, 567 .mu.mol/L; DF ID50, >1000 .mu.mol/L. The toxicity of L1 in vitro was similar for marrows from 3 normal donors and for the recovery marrow from a patient with thalassemia major who had experienced agranulocytosis. Further studies are required to elucidate the mechanisms of L1 -induced agranulocytosis.

L45 ANSWER 28 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 120:290049 CA
TI In vivo and in vitro effects of 3-hydroxypyridin-4-one chelators on murine hemopoiesis
AU Hoyes, Katharine P.; Jones, H. Mark; Abeysinghe, Rajeewa D.; Hider, Robert C.; Porter, John B.
CS Middlesex Sch. Med., Univ. Coll., London, UK
SO Experimental Hematology (New York, NY, United States) (1993), 21(1), 86-92
CODEN: EXHMA6; ISSN: 0301-472X
DT Journal
LA English
AB The effects of 3-hydroxypyridin-4-one (HPO) iron chelators and desferrioxamine (DFO) on murine hemopoiesis in vivo and in vitro have been compared in order to investigate the mechanism by which leucopenia in mice and granulocytopenia in man occurs with 1,2,dimethyl-HPO (CP20). Administration of 60 doses of 200 mg/kg CP20 to Balb/c mice resulted in

significant anemia, lymphopenia and granulocytopenia accompanied by bone marrow hypocellularity. DFO and CP94 (1,2,diethyl-HPO) at the same dose also caused lymphopenia but marrow cellularity was unaffected. When marrow from untreated mice was incubated with HPOs and DFO, erythroid burst-forming cells (BFU-E) and granulocyte/macrophage colony forming units (CFU-G+Mac), colony growth was inhibited in a dose-dependent manner at micromolar concns. The addn. of iron to sat. the chelators abrogated the effects of DFO, but not those of the HPOs. With the HPO-iron complexes, addn. of sufficient iron to sat. the transferrin in the **medium** reversed the inhibitory effects of the relatively hydrophilic CP20-iron complex but not those of the more lipophilic CP94-iron complex. Addn. of further iron-satd. transferrin also cor. inhibition by the CP94-iron complex. These results show that HPO-iron complexes potentially have antiproliferative effects unlike DFO-iron complex (FO). The difference in the relative effects of CP20 to CP94 on hemopoiesis in vivo and in vitro suggests that addnl. factors to those inhibiting hemopoiesis in marrow **cultures** may operate with the long-term administration of iron chelators in vivo.

L45 ANSWER 29 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 118:52399 CA
TI Antioxidant and free radical scavenging activities of the iron chelators pyoverdin and hydroxypyrid-4-ones in iron-loaded hepatocyte **cultures**: comparison of their mechanism of protection with that of desferrioxamine
AU Morel, Isabelle; Cillard, Josiane; Lescoat, Gerard; Sergent, Odile; Pasdeloup, Nicole; Ocaktan, Aydin Z.; Abdallah, Mohamed A.; Brissot, Pierre; Cillard, Pierre
CS Lab. Biol. Cell. Veg., UFR Sci. Pharm., Rennes, 35043, Fr.
SO Free Radical Biology & Medicine (1992), 13(5), 499-508
CODEN: FRBMEH; ISSN: 0891-5849
DT Journal
LA English
AB The protective effect on iron-supplemented hepatocyte **cultures** of three iron chelators, pyoverdin Pa and hydroxypyrid-4-one derivs. CP20 and CP22, was compared to that of the widely known desferrioxamine B (Desferal: DFO), on the basis of two criteria: (a) their effectiveness in inhibiting free malondialdehyde (MDA) prodn. as an index of iron-induced lipid peroxidn.; and (b) their ability to reduce intracellular enzyme leakage. In view of these two markers of iron toxicity, the protective effect of these chelators are classified as follows: DFO > CP20 .gtoreq. CP22 > Pa. The mechanism of cellular protection was elucidated by investigating both the iron-chelating activity and the free radical scavenging property of these agents. As concerns the iron chelation, DFO and Pa exerted the same rank order as for cytoprotection (DFO > Pa). The free radical scavenging property toward hydroxyl radical .bul.OH and peroxyl radical ROO.bul. was investigated in a cell-free exptl. model. The two siderophores, DFO and Pa, appeared to have a lower antiradical activity toward .bul.OH than hydroxypyrid-4-one CP22. This .bul.OH scavenging activity was classified as follows: CP22 .mchgt. Pa > DFO. Moreover the chelators exhibited for the quenching of ROO.bul. the same order of effectiveness as that obsd. for cellular protection: DFO > CP20 .gtoreq. CP22 > Pa. These data indicate that, in addn. to the iron-chelating activity which represents the most important property for detg. the protection capacity of these iron chelators, their free radical scavenging ability also must be taken into account. This direct demonstration of a strong assocn. between the free radical scavenging activity and the protective effect of iron chelators further increases the prospects for the development and clin. applications of new oral chelating drugs.

L45 ANSWER 31 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 115:64014 CA
TI Iron mobilization from myocardial cells by 3-hydroxypyridin-4-one

chelators: studies in rat heart cells in **culture**
AU Hershko, C.; Link, G.; Pinson, A.; Peter, H. H.; Dobbin, P.; Hider, R. C.
CS Dep. Med., Shaare Zedek Med. Cent., Jerusalem, Israel
SO Blood (1991), 77(9), 2049-53
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English
AB The ability of 3-hydroxypyridine-4-ones (I, R1 = Me, C2H5; R2 = Me, CH2CH2OH, CH2CH2OMe, C2H5), a family of bidentate orally effective iron chelators, to remove iron and to prevent iron-induced peroxidn. was studied in beating rat myocardial cells in **culture**. The iron(III) binding const. (log .beta.3) of I is 36, but their lipophilicity may be modified by altering the length of the R2 substituent on the ring nitrogen. There was a direct relation between lipid soly. and chelating efficiency. Although at high concns. I were more effective in iron mobilization than deferoxamine, the opposite was true for low concns. Further studies with 1,2-diethyl-3-hydroxypyridin-4-one (CP94), the most effective of I, have shown that iron mobilization is completed within 6 h, that effective mobilization requires a drug: iron molar ratio exceeding 3:1 permitting the formation of a hexadentate complex, and that the beneficial effects of iron mobilization are manifested in a marked redn. in membrane lipid peroxidn. as indicated by cellular malonaldehyde content. This study represents the first demonstration of a direct interaction between myocardial cells and an orally effective iron chelator, and underlines the need for high molar concns. for achieving an optimal therapeutic effect.

L45 ANSWER 33 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 110:150013 CA
TI Release of iron from ferritin molecules and their iron-cores by 3-hydroxypyridinone chelators in vitro
AU Brady, M. C.; Lilley, K. S.; Treffry, A.; Harrison, P. M.; Hider, R. C.; Taylor, P. D.
CS Krebs Inst. Biomol. Res., Univ. Sheffield, Sheffield, S10 2TN, UK
SO Journal of Inorganic Biochemistry (1989), 35(1), 9-22
CODEN: JIBIDJ; ISSN: 0162-0134
DT Journal
LA English
AB Ferritin mols. contain 24 subunits forming a shell around an inorg. Fe-core. Release of Fe(III) from ferritin and its isolated Fe-cores by a series of hydroxypyridinone chelators with high affinities for Fe(III) was compared. The results collectively suggest that the chelators act by penetrating the protein shell and interacting directly with the Fe-core in ferritin. Fe(III) is probably removed bound to a single ligand, but once outside the protein shell, the trihydroxypyridinone Fe(III) complex predominates. The order of effectiveness of a group of pyridinones found for Fe removal from ferritin mols. in soln. differs from that obtained with hepatocytes in **culture** or with whole animals, where membrane soly. and other factors may modulate the response.

L45 ANSWER 34 OF 35 CA COPYRIGHT 2003 ACS on STN
AN 110:18109 CA
TI Iron mobilization from hepatocyte monolayer **cultures** by chelators: the importance of membrane permeability and the iron-binding constant
AU Porter, J. B.; Gyparaki, M.; Burke, L. C.; Huehns, E. R.; Sarpong, P.; Saez, V.; Hider, R. C.
CS Dep. Clin. Haematol., Univ. Coll. London, London, Wc1E 6HX, UK
SO Blood (1988), 72(5), 1497-503
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English
AB A series of bidentate 3-hydroxypyridin-4-one (I; R1 = Me or Et; R2 = alkyl) Fe chelators that have therapeutic potential as oral Fe chelators

were studied to det. which properties are the most crit. for the mobilization of rat hepatocyte Fe. The relationship between lipid soly. of the free and complexed forms of each chelator and hepatocyte Fe release was investigated, as well as the contribution of the binding const. for Fe(III). I that were approx. equally sol. in lipid and aq. phases were the most active compds., the partition coeff. of the free chelator appearing to be more crit. than that of the complexed form in detg. Fe release. Highly hydrophilic chelators did not mobilize intracellular Fe pools, whereas highly lipophilic compds. were toxic to hepatocytes. The contribution of the binding const. for Fe(III) to cellular Fe release was assessed by comparing I and hydroxypyridin-2-ones, which possess similar partition coeffs. The binding for Fe(III) was particularly important at low concns. of chelator (<100 .mu.M); at higher concns. (>500 .mu.M), Fe mobilization was limited by the available chelatable pool. Measurement of Fe release with other chelators confirmed the importance of both the lipid solubilities and Fe(III)-binding consts. for Fe mobilization. The most active I released more hepatocyte Fe than did deferoxamine when compared at equimolar concns. The ability of an Fe chelator to enter the cell seems to be crucial for effective Fe mobilization, but once within the cell the binding const. of the chelator for Fe(III) becomes a dominant factor.

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L31 ANSWER 22 OF 32 CA COPYRIGHT 2003 ACS on STN
AN 115:64014 CA
TI Iron mobilization from myocardial cells by 3-hydroxypyridin-4-one chelators: studies in rat heart cells in **culture**
AU Hershko, C.; Link, G.; Pinson, A.; Peter, H. H.; Dobbin, P.; Hider, R. C.
CS Dep. Med., Shaare Zedek Med. Cent., Jerusalem, Israel
SO Blood (1991), 77(9), 2049-53
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English
AB The ability of 3-hydroxypyridine-4-ones (I, R1 = Me, C2H5; R2 = Me, CH2CH2OH, CH2CH2OMe, C2H5), a family of bidentate orally effective iron chelators, to remove iron and to prevent iron-induced peroxidn. was studied in beating rat myocardial cells in **culture**. The iron(III) binding const. (log .beta.3) of I is 36, but their lipophilicity may be modified by altering the length of the R2 substituent on the ring nitrogen. There was a direct relation between lipid soly. and chelating efficiency. Although at high concns. I were more effective in iron mobilization than deferoxamine, the opposite was true for low concns. Further studies with 1,2-diethyl-3-hydroxypyridin-4-one (CP94), the most effective of I, have shown that iron mobilization is completed within 6 h, that effective mobilization requires a drug: iron molar ratio exceeding 3:1 permitting the formation of a hexadentate complex, and that the beneficial effects of iron mobilization are manifested in a marked redn. in membrane lipid peroxidn. as indicated by cellular malonaldehyde content. This study represents the first demonstration of a direct interaction between myocardial cells and an orally effective iron chelator, and underlines the need for high molar concns. for achieving an optimal therapeutic effect.

L31 ANSWER 26 OF 32 CA COPYRIGHT 2003 ACS on STN
AN 110:18109 CA
TI Iron mobilization from hepatocyte monolayer **cultures** by chelators: the importance of membrane permeability and the iron-binding constant
AU Porter, J. B.; Gyparaki, M.; Burke, L. C.; Huehns, E. R.; Sarpong, P.; Saez, V.; Hider, R. C.
CS Dep. Clin. Haematol., Univ. Coll. London, London, Wc1E 6HX, UK
SO Blood (1988), 72(5), 1497-503
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English
AB A series of bidentate 3-hydroxypyridin-4-one (I; R1 = Me or Et; R2 = alkyl) Fe chelators that have therapeutic potential as oral Fe chelators were studied to det. which properties are the most crit. for the mobilization of rat hepatocyte Fe. The relationship between lipid soly. of the free and complexed forms of each chelator and hepatocyte Fe release was investigated, as well as the contribution of the binding const. for Fe(III). I that were approx. equally sol. in lipid and aq. phases were the most active compds., the partition coeff. of the free chelator appearing to be more crit. than that of the complexed form in detg. Fe release. Highly hydrophilic chelators did not mobilize intracellular Fe pools, whereas highly lipophilic compds. were toxic to hepatocytes. The contribution of the binding const. for Fe(III) to cellular Fe release was assessed by comparing I and hydroxypyridin-2-ones, which possess similar partition coeffs. The binding for Fe(III) was particularly important at low concns. of chelator (<100 .mu.M); at higher concns. (>500 .mu.M), Fe mobilization was limited by the available chelatable pool. Measurement of Fe release with other chelators confirmed the importance of both the lipid solubilities and Fe(III)-binding consts. for Fe mobilization. The most active I released more hepatocyte Fe than did deferoxamine when compared at equimolar concns. The ability of an Fe chelator to enter the cell seems to be crucial for effective Fe mobilization, but once within the